

Rapid Diagnostic Testing for HIV – Clinical Implications

a report by

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Introduction

The worldwide human immunodeficiency virus (HIV) pandemic has been devastating to date. At the end of 2003 an estimated 40 million people were living with HIV or acquired immunodeficiency syndrome (AIDS). Approximately 14,000 people are thought to be infected daily, with over five million people becoming infected in 2003.¹ Between 800 and 900,000 individuals in the US are living with HIV and there are an estimated 40,000 new infections each year.²

As a central premise, HIV counselling and testing needs to be integrated into the routine medical care of patients.³ It should be offered to all pregnant women, all persons with a possible acute occupational exposure, all patients with a known sexual or needle-sharing exposure to the virus, patients in settings serving populations at increased behavioural or clinical risk and to all patients in areas in which the prevalence of HIV is 1% or greater. Patients with a self-reported HIV risk behaviour, such as injection drug use, homosexual intercourse and unprotected vaginal or anal intercourse with more than one sexual partner – or with a partner who may be infected with HIV – should also be offered counselling and testing, as should patients who specifically request an HIV test. Patients with clinical signs or symptoms of HIV disease (e.g., fever, illness of unknown origin, oral thrush, unexplained lymphadenopathy with or without weight loss, or psoriasis) should be offered counselling and testing. In addition, patients with a diagnosis suggesting increased risk of HIV disease such as opportunistic infections, tuberculosis, cervical or anal cancer, Kaposi's sarcoma, lymphoma, recurrent pneumonia or bacteraemia, hepatitis B, hepatitis C, or a sexually transmitted disease should be offered counselling and testing.^{4,5}

The major focus of HIV prevention and control has been to promote the acceptance of risk-reducing behaviours, through prevention, counselling and testing, and to facilitate linkage to medical, prevention and other supports services.³ Testing has played a major role in reducing the transmission of HIV. Antibody testing to diagnose HIV was introduced in

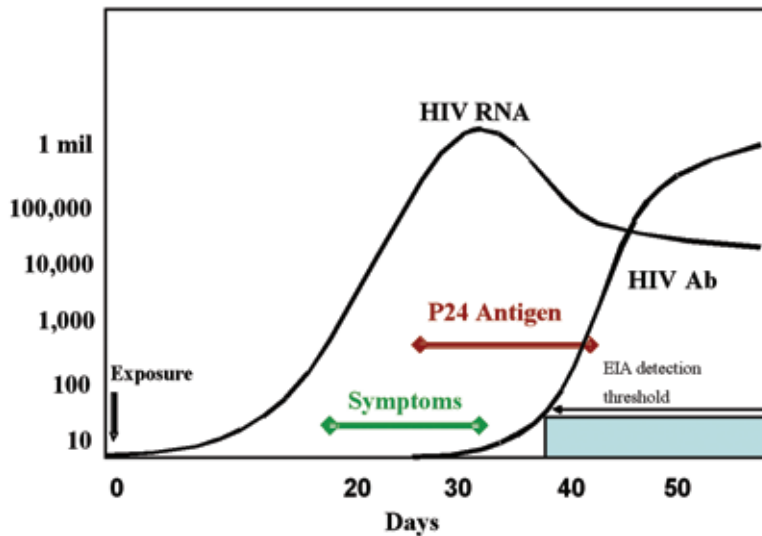
1985.⁵ At that time, most available technologies employed a methodologic paradigm that made use of central facilities equipped with highly-trained technologists performing tests in batches. Such an approach allowed facilities to develop effective quality control techniques to ensure the reliable performance of tests, but also led to infrequent testing and long turn-around times. The standard laboratory HIV testing protocol, which evolved in the 1990s, involved obtaining a blood specimen from the client and sending it to a licensed laboratory for testing. Most often, the central laboratory would perform an enzyme-linked immunoassay (EIA), in order to ensure that a reactive result was due to HIV exposure. A second, more specific assay, the Western blot, was widely used to confirm results. The patient would then need to return for a second visit to receive test results. Unfortunately, many patients would not return for their test results. The lag time between obtaining a specimen and providing results is a time of high anxiety and significant stress for many of these patients. While the time to perform an HIV antibody test is typically a few hours, the time required by the testing paradigm was typically two days to two weeks. Such long delays and the accompanying anxiety clearly contributed to the near 30% of patients who failed to return to counselling centres for their results.

The early and rapid diagnosis of HIV began to assume particular importance as effective combination anti-retroviral therapy became available. Combination therapy contributes to reducing the risk of vertical and occupational HIV transmission while improving the quality of life and the longevity of people infected with HIV. A significant reduction in the lag time between risk exposure and the availability of testing results required the evolution of a new approach to HIV testing – the rapid HIV test. These tests are widely available internationally, including four that have been approved by the US Food and Drug Administration (FDA).

Due to the fact that rapid, point-of-care testing offers the advantage that people do not need to return to obtain their test results, more people know their HIV status and if infected can be referred for treatment,

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Figure 1: The HIV Infection 'Window'



prevention programs and social services more rapidly. People who know they are infected with HIV are more likely to practise risk-reduction, especially if a brief behavioural intervention is conducted at the patient visit.³ Rapid testing offers the advantage of providing test results at the time of the behavioural intervention.

Rapid diagnostic HIV testing has several clinical applications. This paper describes rapid testing and its role in:

- reducing vertical HIV transmission for women who present in labour with unknown HIV status;
- reducing the risk of occupational transmission of HIV; and
- assisting in the diagnosis and counselling of patients with HIV.

Rapid testing plays a crucial role in time-sensitive decisions regarding the need for prophylaxis to reduce transmission in cases of occupational exposures and women presenting in labour with unknown HIV status.⁶

Rapid Diagnostic HIV Tests

Rapid tests to detect the HIV antibody are designed to allow healthcare providers to supply definitive negative and preliminary positive results in minutes at the time of an initial patient visit. In comparison, traditional enzyme immunoassays (EIAs) operate with a paradigm that requires specimen transmittal to a laboratory, the creation of batches of specimens for efficient, cost-effective processing, the use of expensive semi-automated or automated equipment and the presence of significant operator expertise to perform properly

and reliably. These requirements often delay results from reaching the patient for as much as one to two weeks.⁷ Rapid HIV tests are comparable in sensitivity and specificity with traditional EIAs, but can be performed by testing personnel with limited technical expertise in as little as 10 minutes.

A number of HIV tests are being used throughout the world. In the US, four rapid tests have been approved by the FDA for commercial use:

- the Single Use Diagnostic System for HIV-1 (SUDS, Abbott Laboratories, Abbott Park, IL – no longer marketed);
- OraQuick HIV-1 and the Oraquick Advance HIV-1/HIV-2 (Orasure Technologies, Bethlehem, PA);
- Reveal™ (MedMira Laboratories, Halifax, Nova Scotia); and
- Unigold Recombigen (Trinity Biotech plc, Wicklow, Ireland).

Additional rapid tests are under consideration by the FDA. Many candidate rapid tests use a variety of specimen samples including serum, whole blood, plasma and/or oral mucosal transudate (OMT). Using whole blood, the four FDA-approved rapid tests have sensitivities ranging from 95.3% to 100% and specificities ranging from 96.7% to 100%. Performance results of six rapid tests – commercial tests using plasma as the test specimen – demonstrate sensitivities ranging from 96.7% to 100% and specificities ranging from 98.5% to 100%.⁸

The sensitivity and specificity of most rapid assays are comparable to those of non-rapid EIAs. In low-prevalence settings, the predictive value of a single rapid negative test result is very high. A negative rapid test does not, therefore, require further testing and negative results with result-specific counselling can be provided to most people at the time of their initial visit. Due to the fact that the positive predictive value varies with prevalence of HIV infection in the population tested, however, the positive predictive value will be low in populations with low prevalence.⁸ This phenomenon has led to a testing strategy requiring a reactive EIA or rapid test to be confirmed by a second, independent supplemental test.⁹ In studies conducted outside the US, specific combinations of two or more different rapid HIV assays have provided results as reliable as those from the EIA/Western blot combination, which is currently in widespread use.¹⁰ In the US, current recommendations require confirmatory testing to be conducted utilising a Western blot or an immunofluorescence assay (IFA).¹¹

The ‘window’ of HIV diagnosis is dependent upon the diagnostic approach utilised to detect its presence. Following exposure, entry of the HIV virus into the bloodstream typically occurs between three and seven days later with detectable HIV-1 ribonucleic acid (RNA) being demonstrated between seven and 14 days later. A detectable p24 antigen may be present between 12 and 19 days, but antibody seroconversion and detection occurs between 30 and 60 days post-exposure. The onset of symptoms typically occurs three to four weeks post-exposure and most patients are symptomatic with a flu-like illness at the time of antibody seroconversion.

The ease of performing some rapid tests led their manufacturers to seek and be granted waived test status under the federal Clinical Laboratory Improvement Amendments (CLIA). CLIA waived status allows testing facilities to offer HIV testing with less restrictive regulatory requirements. In order to ensure a high-quality testing environment, however, the FDA has limited the test to registered laboratories and requires that the facility institute a quality assurance program. Guidelines from the US Centers for Disease Control and Prevention (CDC) recommend participation in a proficiency-testing program.⁷

Recommendations for Rapid Testing of Women in Labour

Prevention of vertical HIV transmission has been an important success story in the HIV pandemic. The risk of transmission has been reduced from approximately 25% to less than 2% by using currently recommended obstetrical interventions and pre-natal combination anti-retroviral therapy in women aware of their HIV infection early in pregnancy.⁶ Different state and local regulations specify policies and procedures related to HIV counselling and the testing of pregnant women.

Ideally, all pregnant women should be offered HIV testing during an initial pre-natal visit, to allow for timely initiation of treatment to reduce the chance of vertical transmission. A particular area of concern, however, is women who present in labour with unknown HIV status (HIV test results not documented on medical records). These women may not have been offered or opted for HIV counselling and testing during pregnancy or may not have received pre-natal care. Clinical trial data have shown that anti-retroviral medications, even when administration began during labour and delivery and continued in the neonatal period, can reduce mother-to-child HIV transmission by up to 50%.¹²⁻¹⁴ When women present in labour with unknown HIV status, the key to maximal peri-natal HIV risk reduction is rapid testing and initiation of short-course therapy. The CDC-sponsored Mother-Infant

Rapid Intervention at Delivery (MIRIAD) study showed that offering voluntary HIV testing during labour is feasible in obstetrical settings. In addition, point-of-care testing has been shown to provide results faster than sending specimens to the hospital laboratory for rapid HIV testing.¹⁵ The CDC recommends rapid HIV testing for women in labour whose HIV status is unknown.¹⁶

Women in labour who have a preliminary positive rapid test should be offered short-course therapy. One recommendation describes four options for short-course therapy.¹² Both the woman and the child should be referred for follow-up, preferably by providers with experience and expertise in treating HIV.

Recommendations for Rapid Testing Following Potential Occupational HIV Exposure

Transmission of blood-borne pathogens is an occupational hazard for healthcare workers. The average risk of HIV infection from all types of percutaneous exposures to HIV-infected blood is approximately 0.3%. The CDC conducted a case-control study to determine the risk of HIV infection from different types of percutaneous exposures. This case-controlled study showed that the risk of HIV-infection exceeded 0.3% for exposures that involved a deep injury to the healthcare worker, visible blood on the device that caused the injury, a device that had been placed in the source patient’s vascular system, (e.g., a needle used for phlebotomy) or a source patient who died as a result of AIDS within 60 days post-exposure.¹⁷

The average risk of HIV infection following a mucous membrane or skin exposure is less than the risk associated with a percutaneous exposure. After a mucous membrane exposure the average risk of HIV infection is 0.09%. The average risk of HIV infection after a skin exposure is less than 0.09%. The risk of skin exposure may be increased if skin contact is prolonged, if contact involved an extensive area of the skin, if the integrity of the skin is not intact or if the exposure involves a higher titre of HIV.¹⁷

Following a high-risk occupational exposure, employers need to provide healthcare workers with a system for prompt evaluation, counselling and follow-up. First aid needs to be administered immediately after an exposure. Puncture wounds and other cut injuries should be washed with soap and water. If oral and/or nasal mucosa have been exposed, they should be decontaminated by flushing with water. Eyes should be irrigated with clean water and saline or sterile irrigants that are designed for flushing eyes. The exposure should be reported

to the person or department responsible for managing exposures (e.g., employee health or infection control).¹⁸

A key to reducing the risk of occupational HIV transmission is to provide post-exposure prophylaxis (PEP) as soon as possible following a potential exposure. Testing to determine the HIV status of the source of the exposure should be conducted as soon as possible after the incident. The exposure source should receive pre- and post-test counselling and should give consent for HIV testing. A rapid HIV antibody test kit approved for use in the jurisdiction should be considered, particularly if testing by EIA cannot be completed in 24 to 48 hours. Positive results by EIA or rapid HIV antibody tests are considered to be highly suggestive of infection, whereas a negative result is an excellent indicator of the absence of the HIV antibody. Confirmation of a reactive result by Western blot or IFA is not necessary to make initial decisions regarding post-exposure management, but they should be completed before informing the source person.^{17,18}

HIV antibody tests should be performed on the exposed employee immediately to establish a baseline and then periodically for at least six months post-exposure, e.g., six weeks, 12 weeks and six months. HIV testing should be performed on any healthcare worker who has an illness compatible with an acute retroviral syndrome following an occupational exposure, regardless of the interval since the exposure. HIV antibody testing using EIA should also be used to monitor for HIV seroconversion. The routine use of direct assays, e.g., HIV antigen EIA or polymerase chain reaction for HIV RNA, to detect infection in healthcare workers is generally not recommended. The reliability of HIV RNA testing to detect very early infection has not been determined and it is not FDA-approved for this purpose. The employee should be counselled on precautions to prevent the secondary transmission of HIV.¹⁷

If appropriate, CDC recommendations for PEP with laboratory monitoring should be offered to the employee. Although animal studies suggest that PEP is probably substantially less effective when started more than 24 to 36 hours post exposure, the interval after which no benefit is gained from PEP for humans is undefined. In humans, the interval within which PEP should be initiated for optimal efficacy is not known. If appropriate for the exposure, therefore, PEP should be started even when the interval since exposure exceeds 36 hours. Initiating therapy after a longer interval (e.g., one week) might be considered for exposures that represent an increased risk of transmission.¹⁹

Diagnostics of Patients Using Rapid HIV Diagnostic Testing

The CDC currently recommends that all providers integrate HIV counselling and testing into routine practice.³ The use of rapid tests in clinical care settings can substantially improve the delivery of HIV counselling and testing services, because patients can receive their results the same day. A major issue in the US has been patients who present for HIV counselling and testing, who do not return to receive their test results and post-test counselling. The CDC reported that of 2.5 million persons tested in 1995, 25% of those testing positive and 33% of those testing negative did not receive their test results. CDC calculated that a total of 697,495 more people nationwide would have learned their HIV status if rapid testing was used.²⁰

Integration of rapid testing in daily practice can allow prompt diagnosis of patients with HIV. These patients can then be referred to a provider with experience and expertise treating HIV patients. In addition, these patients can be referred for prevention and social services.

Interpretation of Rapid Test Results

Interpretation of rapid tests is the same as other HIV screening tests. A negative result from a single test is interpreted as being negative although, as with other HIV screening tests, if a person may have been exposed to HIV within three months of the test, a repeat test at a later time is recommended. A positive (or reactive) result is considered to be a preliminary positive test result. This must be confirmed using a Western blot or an IFA. This confirmatory testing should be done as soon as possible. If the rapid test is a preliminary positive and the confirmatory test is negative (discrepant results), both the rapid test and the confirmatory test should be repeated. A consultation with an infectious disease specialist is recommended. If the rapid test does not provide a valid test result, it is likely that the test kit did not work properly – in this case, the rapid test should be repeated.¹¹

Counselling Patients with a Negative Rapid Test

Patients whose rapid HIV test result is negative can be told that they are not infected, unless they have had a recent (within three months) known, or possible, exposure to HIV.

Retesting should be recommended for these patients, because sufficient time needs to elapse in order for the development of the antibodies (which are detected by the test) to progress.^{16,21}

Counselling Patients with a Preliminary Positive Rapid Test

Confirmatory testing is always required to confirm a reactive rapid test result. The challenge is providing reactive (preliminary positive) results to patients without the benefit of a same-day confirmatory test. For all patients with a reactive rapid HIV test result, however, it is essential to:

- explain that this is a preliminary test and results need to be confirmed;
- emphasise the importance of confirmatory testing and schedule a return visit for the confirmatory test results; and
- underscore the importance of taking precautions to avoid the possibility of transmitting infection to others while awaiting results of confirmatory testing.²¹

Conclusion

Rapid diagnostic HIV testing will improve the proportion of patients who receive their test results, help with clinical decision-making regarding the use of short course anti-retroviral therapy to reduce the risk of vertical HIV transmission for women who present in labour with unknown HIV status, and help determine the need for PEP for potential occupational exposures to HIV.^{16,17} As HIV counselling, testing and referrals advance, it is imperative that adjustments be made in recommendations and practices.

People found to be infected with HIV should be referred for medical care by a provider with experience and expertise treating HIV disease and be referred for prevention services and social services. HIV/AIDS reporting requirements should be followed. ■

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